I. REMARKS

Claims 1 – 20 and 22 are pending in the above-identified application. Examiner indicates that Claim 20 is allowed and that Claims 7 and 10-16 are objected to as being dependent upon a rejected base claim but would be allowable if rewritten in Independent form. As fully discussed below, Applicants contend that amended Claim 1 (the rejected base claim) is allowable and thus, Claims 1 and 10 – 16 are allowable as presently presented. Independent Claims 1, 20 and 22 are amended herein to limit the definition of "respiratory tract" to the "lower respiratory tract". The amendment is supported by Applicants' specification at p.8, lines 1-11. Also, the term "lower respiratory tract" is an art recognized term as evidenced by the attached print-out from the MEDLINEplus web-site accessible at **www.nlm.nih.gov**. Accordingly, the amendment is proper. For Examiner's information, in January, the assignee of the above-identified application changed its name from BattellePharma, Inc. to Ventaira Pharmaceuticals, Inc.; our web site is **www.ventaira.com**.

II. ARGUMENTS

A. Rejection Under 35 USC § 103(a)

Examiner has rejected Claims 1-6, 8, 9, 17-19 and 22 under 35 USC §103(a) as being obvious over Modi et al. (US Pat. 5,653,987). Examiner contends that:

- Modi teaches a liquid formulation for nasal delivery to a patient comprising water (carrier), protein (insulin, cytokin), sodium lauryl B-D-maltopyranoside (derivatized carbohydrate) and other compounds such as oleic acid (excipient) and antioxidant (excipient); and
- It would be obvious to the skilled artisan to determine the optimum amounts of carrier, organic solvent, and excipient to develop a composition that would be effective in treatment.

The liquid formulation described and claimed by Modi is an aqueous liquid formulation that is meant to be delivered orally (ingested) to the gastrointestinal tract not aerosolized and delivered to the lung via inhalation of an aerosol. Although, the aqueous liquid formulations of Modi are specifically developed for oral dosing they may be administered to the nose. However,

Modi recognizes that nasal delivery could cause sneezing or dripping as a result of irritation to the sensitive lining of the nose. See Col 1, lines 46-52.

Although Modi teaches that the claimed formulations maybe delivered nasally as well as orally, it is clear from the context of the reference that Modi contemplates conventional nasal delivery such as a nasal spray or nose drops. Further, Modi acknowledges that nasal delivery has problems such as irritation of the mucous membranes of the nasal passages by the absorption enhancers and dripping of the drug from the nose. Where it is important that the amount of the administered dose of the drug is the same as the dose that is actually delivered as in the case of insulin, nasal delivery is not a very precise method of delivering the drug.

The aqueous formulations of Modi are required to contain at least two absorption enhancing compounds selected from specific combinations. See Col 2, lines 12-63. The purpose of the absorption enhancer is to enhance the solubility of the active agent (drug) in the stomach and the absorption of the drug across the intestinal wall. Col 1, lines 53-61.

Example II and Table III of Modi illustrate the importance of using at least two absorption enhancing compounds selected from the specific combinations described by Modi. In Example II, a composition containing only one absorption enhancer was tested. The data in Table III shows that an orally administered insulin formulation containing only sodium cholate as the absorption enhancer had little metabolic effect on blood glucose levels.

One skilled in the art is taught by Modi that the presence of at least two absorption enhancers is essential and that the preferred combinations are a combination of a salt or ester of a bile salt e.g. deoxycholate or chenodeoxycholate and a surface active agent e.g. sodium lauryl sulfate or polyoxyethylene 9-lauryl ether. Col 3, lines 12-19; the preferred combination of Modi is the bile salts deoxycholate and chenodeoxycholate and the surface active agent, polyoxyethylene 9-lauryl ether.

The use of absorption enhancers in oral drug formulations was known prior to the work of Modi. It was known in the art as early as 1990-1991 that:

> "The intestinal absorption of water-soluble drugs is... limited by... poor membrane permeability... absorption enhancers have been often adopted to

> improve absorption of... poorly absorbable drugs, including... peptide and protein drugs... absorption enhancers included surfactants, bile salts, chelating agents and fatty acids (Lee and Yamamoto (1990) and Lee *et al.* (1991) cited in Yamamoto *et al.*, Modulation of Intestinal Permeability by Nitric Oxide donors: Implications in Intestinal Delivery of Poorly Absorbable Drugs, The J. of Pharmacology and Experimental Therapeutics, Vol, 296, (2001), pp. 84-90 at p. 84.)

Examiner is correct that the Modi reference at Col. 2, line 24-25, describes N-lauryl –B-D-maltopyranoside (N-dodecyl-B-D-maltopyranoside) as being a possible absorption enhancer. However, the reference also teaches that one must use at least two absorption enhancers to get the desired effect. N-dodecyl-β-D-maltopyranoside is an example of a "derivatized carbohydrate" as described by Applicants' specification. However, Applicants do not claim any derivatized carbohydrate *per se*. What applicants claim is a specific stable liquid formulation of a therapeutically active protein that is useful for aerosol delivery via inhalation to the lungs of a patient in need of treatment.

N-dodecyl-β-D-maltopyranoside is a surface active agent which has many potential uses. The issue is whether there is any direction provided by Modi which would lead the skilled artisan to conclude that one might use N-dodecyl-β-D-maltopyranoside as a stabilizer for liquid formulations of proteins or peptides which are useful for aerosolization and inhalation. Modi certainly does not suggest that N-dodecyl-β-D-maltopyranoside may be used as the only absorption enhancer in the Modi formulations. In fact, Modi does not teach that N-dodecyl-β-D-maltopyranoside is a preferred surface active agent for use in the combinations of absorption enhancers taught by the reference.

The problems associated with oral delivery of a protein or peptide are quite different from those associated with the administration of an aerosolized liquid solution or suspension of a protein or peptide to the lungs of a patient. Oral delivery of a peptide involves getting the drug through the acidic environment of the stomach and into the alkaline upper gastrointestinal region where absorption takes place. Specialized cells in the stomach wall produce large amounts of hydrochloric acid and this means that the stomach is about pH 2. The low pH provides an environment that allows the protease pepsin to be active. The first hurdle facing the pharmaceutical formulator in orally delivering a peptide such as insulin is getting the drug

through the stomach without being broken down by pepsin into smaller fragments. If this hurdle is overcome, the pharmaceutical formulator must still get the therapeutic dose of insulin absorbed across the intestinal wall.

The treatment of the diabetes therapeutic area is worth billions of dollars and many pharmaceutical companies are working on non-injectable formulations of insulin for the treatment of both type 1and and type 2 forms of the disease. Those skilled in the art of oral delivery of drugs still face the threshold issue in oral drug delivery of a protein or peptide, that is, getting the drug through the stomach in its active form. Assuming that this hurdle is overcome, the oral formulation must still allow or the protein or peptide to survive in the alkaline environment of the small intestine and to allow for the drug to cross the intestinal wall. Many approaches are being tried, e.g., modifying the peptide to stabilize it from protease degradation (NOBEX Corporation HIM2 oral insulin drug), and using a poly-amino acid nanoparticles system for controlled-release of native proteins over a period of time (Flamel Technologies' Basulin product). Thee are examples of oral formulations of insulin in human clinical trials. Despite the intense research and development of alternatives to delivery of insulin by injection, there is not one FDA approved oral product on the market.

One skilled in the art of pulmonary drug delivery of an aerosol to the deep lung is not necessarily skilled in the art of formulation a drug for oral delivery and vice versa. There is no teaching or suggestion in Modi that the problems associated with oral drug delivery is the same as that associated with pulmonary drug delivery. There is nothing in Modi that speaks to delivery of a protein or peptide to the lung via inhalation of an aerosol or the development of a liquid formulation suitable for aerosolization.

There is no teaching or suggestion in the Modi reference which would motivate the skilled pharmaceutical formulator to modify the orally active peptide formulations of Modi to the extent necessary to produce the formulations claimed by Applicants. Modi teaches the criticality of a combination of certain absorption enhancing agents. In order to arrive at Applicants' claimed invention, the skilled formulator would have to ignore the essence of what is taught and claimed by the Modi patent. Neither Examiner nor the Modi patent provides any direction or motivation which would lead one skilled in this art to ignore the specific teaching of Modi regarding the criticality of using at least two absorption enhancers selected from various

combinations of bile salts and surfactants. Accordingly, the Modi reference fails to render Applicants' claimed formulation obvious under Section 103(a).

B. Conclusion

Based on the arguments made herein, it is respectfully asserted that Claims 1-20 and 22 directed to a stable liquid formulation of a therapeutically active protein useful for aerosol delivery to the respiratory tract of a patient in need of treatment are in condition for allowance. Examiner is respectfully requested to withdraw the rejections under 35 USC §103(a) and to issue a Notice of Allowance.

Respectfully submitted,

Dated: February 10, 2004

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